Final Report for HTMR Network Grant N79.

Title: Efficient sample schemes for estimation of value of information of future research

Applicants:

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Background:

Cost-effectiveness models are used in health economic decision making to compare the costs and effects of competing strategies for the management of disease. These decision recommendations are uncertain due to limitations in the available evidence. Value of information calculations measure the expected improvement in our decision recommendations, on the monetary scale, if we reduce (Expected Value of Sample Information; EVSI) or eliminate (Expected Value of Partial Perfect Information; EVPPI) uncertainty by gathering further evidence. EVPPI and EVSI can therefore be used to guide research funding decisions and inform trial design. However, as EVPPI and EVSI involve the expectation of a maximum of a conditional expectation, 2-level nested Monte Carlo simulation and sometimes additional Markov chain Monte Carlo (MCMC) simulation is necessary. This is very computationally intensive and often impractical. An additional challenge is that relative treatment effectiveness estimates often come from Bayesian network meta-analyses (NMA). As closed forms for posterior distributions are in many cases difficult to express, Bayesian NMA is usually conducted in the WinBUGS software which generates posterior samples via MCMC. This complicates EVPPI and EVSI as the necessary conditional expectations cannot be explicitly calculated.

Efficient sampling schemes are in wide use in areas outside of medical decision making, such as mathematical finance. This project aimed to assess the potential of these sampling scheme to increase computational speed and improve convergence of nested sampling methods for EVPPI, and EVSI.

Original objectives:

The advanced sampling schemes we aimed to explore were importance sampling, stratified sampling, multilevel Monte Carlo (MLMC), and quasi Monte Carlo (QMC). We also aimed to apply selected methods to two previously developed and real-world example cost-effectiveness models. The first was a model exploring the cost-effectiveness of prescribing anti-depressants by baseline severity, the second explored the cost-effectiveness of oral anticoagulants for the prevention of stroke in atrial fibrillation. This second example was a 25-state Markov model with almost 100 input parameters, many informed by large scale NMAs and MCMC simulations, representing a highly complex and challenging example on which to apply our methods.

What was achieved:

In line with our submitted application to HTMR, we began with a kick-off meeting for the project in January 2017; in addition to the three co-applicants, our collaborators Mike Giles from Oxford University and Christophe Andrieu from Bristol University were also in attendance. We successfully recruited two senior research associates, Wei Fang and Zhenru Wang, to job-share for 9 months on the project. Wei and Zhenru, primarily under the guidance of Howard Thom and Mike Giles but with useful input from Nicky Welton, Chris Jackson, and Christophe Andrieu achieved the following:

- Determined that stratified sampling and importance sampling would be less suitable for efficient EVPPI calculation than MLMC and QMC.
- Applied MLMC and QMC to a very simple cost-effectiveness model of depression; this model was a simple decision tree with (artificially constructed) absolute probabilities, costs, and utilities as inputs. Although unrealistic, this helped Wei and Zhenru to learn cost-effectiveness modelling and Howard and Nicky to better understand MLMC and QMC.
- Applied MLMC and QMC to a more complex depression model. This was a Markov model partially informed by a Bayesian NMA (albeit again artificially constructed).
- MLMC and QMC usually assume the closed form for the posterior distribution is known so novel methods to apply MLMC and QMC to NMA via MCMC outputs were developed. One of these was closed form approximations to the MCMC posterior distributions; another was a form of dimension reduction.
- Using all that was learned, MLMC and QMC were applied to the 25-state Markov model in atrial fibrillation which is informed by a large NMA. This produced EVPPI estimates that could not otherwise be estimated (due to their computational complexity and issues with MCMC) and represented a significant step forward in EVPPI methodology.
- The application of MLMC and QMC to EVSI was not fully developed but potential ways to implement them were considered.

Outputs / Examples of impact:

In November of 2017, Howard Thom presented a poster on our research at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) European Congress in Glasgow. This was titled “Advanced Monte-Carlo Sampling Schemes for Value of Information Estimation” (https://doi.org/10.1016/j.jval.2017.08.2219). ISPOR is one of the largest and most significant health economic modelling conferences where researchers working in academia, industry, and government converged, which ensured a wide audience and high impact for the poster.

We are currently writing up a methods paper describing our findings. We aim to submit to the journal “Medical Decision Making” later this year. The paper will be accompanied by source code to enable other researchers to adopt our methods to their own value of information calculations, greatly increasing its impact.

The application of MLMC to the estimation of EVPPI using the cost-effectiveness of anticoagulants economic model is a significant output of the project; it had previously been infeasible for us to estimate EVPPI for this model due to the high complexity. The results of this EVPPI will be included in a forthcoming paper on the cost-effectiveness of anticoagulants that we are preparing for the journal “Pharmacoeconomics”.

Next Steps (list any future plans):

Howard Thom will present the application of MLMC and QMC to the estimation of EVPPI at a workshop in July 2018.

Howard Thom is currently applying the MLMC approach to a further EVPPI calculation for a trial comparing mechanical/tissue valve with the Ross operation (autograft) for aortic valve replacement in adults. EVPPI calculations will be novel in this area and the results will be included in a forthcoming publication. Chris Jackson may also adapt the MLMC/QMC approaches to EVPPI and EVSI calculations for other applications.

In addition to the above applied work, Howard Thom is currently putting together an application for a Medical Research Council New Investigator Research Grant to adapt the MLMC/QMC sampling schemes to EVSI, with a particular focus on the analysis of trials with adaptive design components.